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10/538,000	06/09/2005	Pieter Jan Arnoldus Maria Plomp	GRT/4662-25	8720

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,000	PLOMP ET AL.	
	Examiner	Art Unit	
	DELIA M. RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,22-26,28,29 and 32-40* is/are pending in the application.

4a) Of the above claim(s) *1-9,26,28,29 and 35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-25,32,34 and 40* is/are rejected.

7)☒ Claim(s) *33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-9, 22-26, 28-29, 32-40 are pending.

Applicant's amendment of claims 1-9, 22-26, 32-36, addition of claims 37-40, and amendments to the specification as submitted in a communication filed on 9/1/2009 are acknowledged.

New claim 40 is directed to the elected subject matter. New claims 37-39 are directed to the non-elected processes of Groups I, II or III (claim 37-Groups I and II; claims 38-39-Group II). This application contains claims 1-9, 26, 28, 29, 35-39 drawn to an invention non-elected with traverse in a communication filed on 1/12/2009. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 22-25, 32-34 and new claim 40 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. The previous objection to the title and the specification for containing hyperlinks is hereby withdrawn by virtue of applicant's amendments.

Claim Objections

2. The previous objections to claims 23-25, 32-34 are hereby withdrawn by virtue of applicant's amendments.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 24, 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This a new rejection necessitated by amendment.

5. Claim 24 is indefinite in the recitation of "an isolated asparaginase obtained by expressing a polynucleotide…..; or a vector comprising said polynucleotide.." for the following reasons. As written, it is unclear if the claim is directed to (1) an asparaginase or a vector, or (2) an asparaginase obtained by expressing a polynucleotide or a vector comprising said polynucleotide, wherein said polynucleotide hybridizes under the conditions recited. For examination purposes, the Examiner will use the second interpretation as indicated above. Correction is required.

6. Claim 34 is indefinite in the recitation of "the isolated asparaginase according to claim 22…and the asparaginase has asparaginase activity" for the following reasons. The preamble of claim 22 recites "an isolated asparaginase...". As such, one would understand that the claimed polypeptide has enzymatic activity, i.e., asparaginase activity. The term "and the asparaginase has asparaginase activity" is unclear and confusing because one cannot determine if it is merely redundant or if the protein of claim 22 does not have asparaginase activity. It is noted that the Examiner has interpreted claim 22 to be drawn to a protein having asparaginase activity. If this interpretation is incorrect, new grounds of rejection may be introduced. Applicant is requested to clearly indicate whether the polypeptide of claim 22 is intended to be a polypeptide having asparaginase activity. Clarification/correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 24, 32 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection necessitated by amendment.

Claim 24 (claims 32 and 40 dependent thereon) has been amended to recite specific hybridization conditions. While the Examiner has been able to find support for high stringency conditions wherein said conditions comprise hybridizing at 68 C in 5X SSC, 5X Denhardt's solution, 1.0% SDS and washing in 0.2X SSC, 0.1% SDS at room temperature or at 42 C, the Examiner has not been able to find support for hybridization conditions that only comprise hybridizing at 68 C in 5X SSC, 5X Denhardt's solution, 1.0% SDS (no washing conditions). Thus, there is no indication that enzymes which are encoded by polynucleotides that hybridize under conditions comprising hybridizing at 68 C in 5X SSC, 5X Denhardt's solution, 1.0% SDS were within the scope of the invention as conceived by Applicant at the time the application was filed. Accordingly, Applicant is required to cancel the new matter in response to this Office Action.

9. Claim 23 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. This rejection as it relates to claim 23 has been discussed at length in the previous Office action mailed on 4/1/2009. The rejection of claim 23 is maintained for the reasons of record and those set forth below.

11. Applicant argues that the specification discloses examples of how to practice the claimed invention with functional equivalents of the polypeptide of SEQ ID NO: 3, therefore applicant submits that one of skill in the art would be in possession of functional equivalents such as 90%/95% sequence identical homologs of the polypeptide of SEQ ID NO: 3 as well as polypeptides encoded by nucleic acids that hybridize under the recited conditions. With regard to the cited art, applicant is of the opinion that the examples provided are exceptional and not indicative of the general case.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claim 23. It is reiterated herein that neither the specification nor the art provides the structural characteristics required in any structural homolog of the polypeptide of SEQ ID NO: 3 having 90% sequence identity to SEQ ID NO: 3 which would allow one of skill in the art to recognize whether such homolog is an *A. niger* asparaginase. As previously indicated, there is no teaching or suggestion in the art or the specification indicating that all *A. niger* asparaginases would have 90% or more sequence identity to SEQ ID NO: 3, or that all *A. niger* asparaginases would comprise SEQ ID NO: 3. In fact, the teachings of Louboudy S. (Egyptian Journal of Biotechnology 4:110-123, 1998; cited in the previous Office action) are further evidence that there is structural/functional variability among asparaginases from *A. niger* since the asparaginase of Louboudy appears to have a different pH optimum from that of the polypeptide of SEQ ID NO: 3, which would strongly suggest that the asparaginase of Louboudy has a different structure than that of the polypeptide of SEQ ID NO: 3 since structure determines function. In view of the fact that the identifying structural features of *A. niger* asparaginases have not been disclosed either in the specification nor the art, one cannot reasonably conclude that the identifying characteristics of the recited genus of *A. niger* asparaginases have been adequately described in the instant application. With regard to the teachings of the cited prior art, it is noted that the references provided are examples which further support the teachings of Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) regarding the unpredictability of determining a priori the

function of structural homologs based solely on structural homology. Thus, contrary to applicant's assertions, these references are not considered "exceptional".

13. Claims 22-25, 32 remain rejected and new claim 40 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the asparaginase of SEQ ID NO: 3, does not reasonably provide enablement for (a) an asparaginase which is at least 90% sequence identical to the polypeptide of SEQ ID NO: 3, (b) any asparaginase encoded by a polynucleotide which hybridizes under the conditions recited in claim 24, or (c) an asparaginase comprising an enzymatically active fragment of (b). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

14. This rejection as it relates to claims 22-25, 32 has been discussed at length in the previous Office action mailed on 4/1/2009. The rejection of claims 22-25, 32 is maintained and further applied to new claim 40 for the reasons of record and those set forth below.

15. Applicant argues that the specification teaches how to make the asparaginases of the claims and confirm their enzymatic activity. According to applicant, the amount of experimentation required to enable the claimed polypeptides would not be undue for skilled artisans familiar with protein engineering.

16. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claim 22-25, 32 or avoid the rejection of new claim 40. While it is agreed that the molecular biology techniques required to make the claimed polypeptides are known in the art, and enzymatic assays are available to test whether a variant has asparaginase activity, the issue at hand is how much experimentation would be required to enable the entire scope of the claims. Using the same calculations provided by the Examiner with regard to 80% sequence identity homologs of the polypeptide of SEQ ID NO: 3, one could determine that the total number of 90% sequence identity homologs of the polypeptide of SEQ ID NO: 3 is $378!x19^{38}/(378-38)!/38!$ (SEQ ID NO:3 has 378 amino acids; 38 amino acids =

0.1x378) or $9.6x10^{100}$ variants. Since nothing is known about the structural features required among all these variants to have asparaginase activity, or the structural features which are characteristic of *A. niger* asparaginases, one of skill in the art would have to test an infinite number of proteins to determine which ones have activity and which ones are naturally found in *A. niger*.

With regard to the polypeptides encoded by the nucleic acids that hybridize to the polynucleotides of SEQ ID NO: 1 or 2 under the recited conditions, it is noted that these polypeptides can have little structural homology with the polypeptide of SEQ ID NO: 3. First, a nucleic acid which hybridizes under the conditions recited to a complement of the polynucleotide of SEQ ID NO: 1 or 2 is a nucleic acid that does not have to hybridize to the full-length complement of the polynucleotide of SEQ ID NO: 1 or 2 since, in the absence of a limitation regarding length, a complement can be a fragment of the full-length complement of the polynucleotide of SEQ ID NO: 1 or 2 that hybridizes under the recited conditions. Thus, the nucleic acid encoding the claimed enzyme can be a nucleic acid which hybridizes to a fragment of any size of the full-length complement of SEQ ID NO: 1 or 2 under the conditions recited. Second, even if one were to interpret the term "complement" as "full-length complement", a calculation of the Tm of the polynucleotide recited in claim 24 shows that under the conditions recited, the recited nucleic acid would have 66.2% sequence identity with the polynucleotide of SEQ ID NO: 1 or 2. Using the well known equation of Meinkoth and Wahl (Current Protocols in Molecular Biology, Hybridization Analysis of DNA Blots, pages 2.10.8-2.10.11, 1993), Tm = 81.5 ºC +16.6x$\log_{10}$[Na+] +0.41x(%GC) - .61x(%form) – 500/L, the corresponding Tm for the polynucleotide recited is approximately 101.8 ºC assuming a G+C content of 50% and neglecting the term 500/L (L=length of polynucleotide) (101.8 ºC = 81.5 + 16.6x$\log_{10}$[3.9x5/20] +0.41x(%50) - .61(%form = 0); for 20xSSC the molar concentration of Na+ is 3.9). As known in the art, Tm is reduced by approximately 1 ºC for each 1% mismatching, therefore under the conditions recited (5xSSC and 68 ºC), this is equivalent to approximately 33.8% mismatching (33.8% = 101.8ºC – 68ºC). This level of mismatching amounts to 384 nucleotides for the polynucleotide

of SEQ ID NO: 2 which can be modified (384 = 0.338x1137) within SEQ ID NO: 2 (1090 nucleotides can be modified within SEQ ID NO: 1; 1090 = 0.338x3223). Since a great number of these mismatches can each affect one codon, a protein encoded by a variant of the polynucleotide of SEQ ID NO: 1 or 2 that hybridizes under the conditions recited can essentially have little structural homology with the polypeptide of SEQ ID NO: 3. For example, out of 384 nucleotide mismatches, 300 can each affect one codon. In that case, such polynucleotide would encode a protein having 20.6% sequence identity to the protein of SEQ ID NO: 3 (20.6% = 100-300x100/378). Testing the essentially infinite number of polypeptides which are encoded by the genus of nucleic acids that hybridize under the conditions recited to the polynucleotides of SEQ ID NO: 1 or 2, or the essentially infinite number of 90% sequence identity homologs of the polypeptide of SEQ ID NO: 3 and determine which ones have asparaginase activity would constitute undue experimentation.

Claim Rejections - 35 USC § 102

17. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

18. Claims 22-25, 32-34 were rejected under 35 U.S.C. 102(b) as being anticipated by Louboudy S. (Egyptian Journal of Biotechnology 4:110-123, 1998). This rejection has been discussed at length in the Office action mailed on 4/1/2009.

19. Applicant argues that the enzyme of the instant application has a different pH optimum and points to Example 2 of the specification as showing the maximum enzymatic activity obtained at pH 5.5 in citric/phosphate buffer. Applicant also argues that the temperature optimum for the enzyme of the instant application is around 50 C whereas that of Louboudy is 30 C.

20. Applicant's arguments have been fully considered. The Examiner was not able to find any reference to the temperature optimum of around 50 C in the specification. However, in view of the fact

that the asparaginase of Louboudy shows maximum enzymatic activity at pH 6.6, 6, and 7.4 in citrate/phosphate, citrate, and Tris-HCl buffers, respectively (Figures 4-6), and Table 2 of the specification shows the maximum enzymatic activity of the enzyme of SEQ ID NO: 3 at pH 5, this rejection is hereby withdrawn.

21. Claims 24, 32 remain rejected and new claim 40 is rejected under 35 U.S.C. 102(b) as being anticipated by Minton et al. (PIR accession number A26064, 1999).

22. This rejection has been discussed at length in the Office action mailed on 4/1/2009. It is maintained for the reasons of record and further applied to new claim 40 for the reasons of record and those set forth below.

23. Applicant argues that the polypeptide of Minton et al. shares a low level of homology with the polypeptide of SEQ ID NO: 3, thus the nucleic acid encoding the polypeptide of Minton et al. would not hybridize under the conditions recited.

24. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 24, 32 or avoid the rejection of new claim 40. Claims 24, 32 and 40 are directed in part to a polypeptide which is encoded by a polynucleotide that hybridizes under specific conditions to the polynucleotide of SEQ ID NO: 1 or 2. As previously noted, the limitation stated in claim 32 is a product-by-process limitation. The patentability of a product recited in a product-by-process format is determined solely by the characteristics of the product (MPEP § 2113). For the reasons extensively discussed above in Claim Rejections under 35 USC 112, first paragraph, the nucleic acid encoding the claimed enzyme can be a nucleic acid which hybridizes to a fragment of any size of the full-length complement of SEQ ID NO: 1 or 2 under the conditions recited. In addition, even if one were to interpret the term "complement" as "full-length complement", as indicated above, a nucleic acid that hybridizes under the conditions recited would have 66.2% sequence identity with the polynucleotide of SEQ ID NO: 1 or 2.

A nucleic acid having 66.2% sequence identity to SEQ ID NO: 2 can potentially encode a protein having little structural homology to the polypeptide of SEQ ID NO: 3 since this level of identity amounts to up to 384 mismatches (384 = 33.8x1137/100), and a great number of these mismatches can each alter a codon. Since the polypeptide of SEQ ID NO: 3 has 378 amino acids, the nucleic acid of claims 24, 32 and 40 can encode a protein which has less than the 43% sequence identity between the protein of Minton et al. and the polypeptide of SEQ ID NO: 3 (43% = 163x100/387; see alignment previously provided). As such, the asparaginase of Minton et al. anticipates the instant claims as written.

Allowable Subject Matter

25. Claim 33 appears to be allowable over the prior art of record but it is objected to as being dependent upon a rejected base claim.

Conclusion

26. No claim is in condition for allowance.

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

28. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

29. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (571) 272-0811. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner
Art Unit 1652

DR
December 28, 2009